The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1721821

RESEARCH ARTICLE

Outcomes of BCG Therapy in Patients with High and Very High-Risk Non-Muscle-Invasive Bladder Cancer: Reassessing EAU Risk Stratification

Özgür Arıkan [1], Ayberk İplikçi [1], Hüseyin Özgür Kazan [1], Ahmet Keleş [1], Ferhat Keser [1], İlkin Hamid-zada [1], Mehmet Çağlar Çakıcı [1], Meftun Çulpan [1], Asıf Yıldırım [1]

[1] Department of Urology, Istanbul Medeniyet University, Istanbul, Türkiye

Submitted: *2025-06-17*
Accepted: *2025-08-06*

Corresponding Author;
Ayberk Iplikci, MD, FEBU

Address: Egitim Mahallesi, Dr. Erkin Cd., 34722 Kadıköy, İstanbul, Türkiye

E-mail: ayberkiplikci@gmail.com

ORCID

O.A.	0000-0002-4647-4864
A.İ.	0000-0002-5822-7799
H.Ö.K.	0000-0003-0202-0454
A.K.	0000-0001-5436-1803
F.K.	0000-0002-2803-6481
I.H.Z.	0009-0000-0550-250X
M.Ç.Ç.	0000-0002-0176-5887
M.Ç.	0000-0001-8573-1192
A.Y.	0000-0002-3386-971X

Abstract

Objective: To evaluate the oncologic outcomes of high-risk (HR) and very high-risk (VHR) non-muscle-invasive bladder cancer (NMIBC) patients treated with Bacillus Calmette-Guérin (BCG) immunotherapy and assess the new European Association of Urology (EAU) risk stratification.

Material and Methods: This retrospective cohort study analyzed data from 211 HR and VHR NMIBC patients treated with BCG therapy between January 2015 and January 2024. Risk stratification was performed using the EAU NMIBC risk calculator. Recurrence, progression, recurrence-free survival (RFS), and progression-free survival (PFS) were assessed.

Results: The cohort comprised 144 (68.2%) HR and 67 (31.8%) VHR patients. The VHR group had significantly more adverse pathological features (larger and multiple tumors, higher pT stage, CIS, variant histology, lymphovascular invasion, tumor necrosis). While there was no significant difference in overall recurrence (33.3% vs. 37.3%, p=0.572) or progression rates (10.4% vs. 9%, p=0.741) between HR and VHR groups, the 5-year RFS was significantly lower in the VHR (56% vs. 75%, p=0.003). The 5-year PFS was similar between the groups (86% vs 91%, p=0.311).

Conclusion: In spite of the fact that the VHR group presented with more aggressive tumor characteristics, BCG therapy resulted in similar overall progression rates compared to the HR group. These findings suggest that the EAU risk stratification may overestimate the risk of progression in BCG-treated patients, particularly those classified as VHR, and that BCG remains a valuable treatment option even in this population.

Keywords: Bacillus Calmette-Guerin (BCG) therapy, EAU risk stratification, non-muscle invasive bladder cancer (NMIBC)

Cite; Arikan O, Iplikci A, Kazan HO, Keles A, Keser F, Hamid-zada I, Cakici MC, Culpan M, Yildirim A. Outcomes of BCG Therapy in Patients with High and Very High-Risk Non-Muscle-Invasive Bladder Cancer: Reassessing EAU Risk Stratification. New J Urol. 2025;20(3):166-174. **doi:** https://doi.org/10.33719/nju1721821

INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) comprises a significant proportion of newly diagnosed bladder cancers (BC) (1). NMIBC is a heterogeneous disease with varying risks of recurrence and progression among patients (2). The presence of this inherent heterogeneity indicates the necessity of accurate risk stratification for patients. Effective risk stratification guides and optimizes the treatment and facilitates patient selection for clinical trials. Previously, the European Association of Urology (EAU) guidelines employed risk stratification for NMIBC patients. This stratification relied on risk tables developed by the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Group. These tables categorized patients into three risk groups: low, intermediate, and high-risk (HR) (3). This stratification system was refined in 2021 to incorporate an additional "very high-risk" (VHR) category (4). Risk stratification system integrates various clinical factors, including patient age, tumor stage and grade, tumor size, multiplicity, and presence of carcinoma in situ (CIS) to estimate the probability of muscle-invasive bladder cancer (MIBC) progression at one, five, and ten years. The new risk stratification system recommends early cystectomy for the VHR group due to their elevated risk of progression (4,5). However, the development of these risk groups excluded patients receiving Bacillus Calmette–Guérin (BCG) immunotherapy, a well-established treatment known to decrease NMIBC progression (4,5). Consequently, the accuracy of these updated risk groups in identifying and guiding management for patients receiving BCG remains undetermined. To address this knowledge gap, our study investigated the comparative outcomes of HR and VHR NMIBC patients who received BCG therapy.

MATERIALS AND METHODS

Study Design and Patient Population

Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee Approved by the Ethics Committee. (Approval No: 2022/0560). All patients participating in the study were informed about the study, and their informed consent was obtained. The study analyzed data from patients diagnosed with BC between January 2015 and January 2024. A total of 1535 patients were initially identified with a diagnosis of BC. Risk stratification was determined using the EAU NMIBC risk calculator, and the patient selection process is detailed in **Figure 1**.

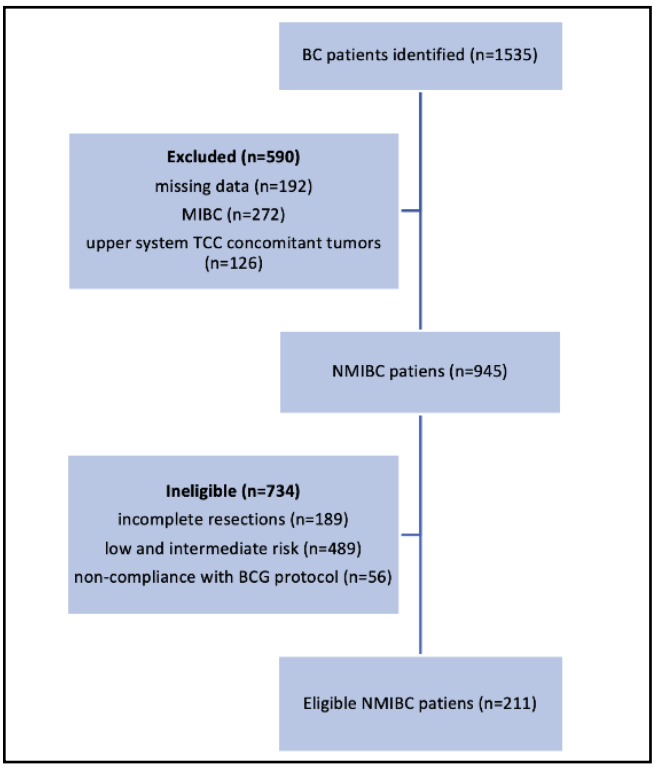

Figure 1. Study flowchart

Initial exclusions included patients with missing data (n=192), MIBC (n=272), and concomitant upper system transitional cell carcinoma (n=126), resulting in 945 patients with NMIBC. Further exclusions were applied based on the following criteria: incomplete resection at the first or second transurethral resection of bladder tumor (TURBT) (n=189), low or intermediate risk disease according to the EAU NMIBC risk calculator (n=489), and non-compliance with the established BCG protocol (n=56). The final study cohort comprised 211 eligible patients with HR or VHR NMIBC. All included patients had a minimum follow-up duration of 12 months.

Treatment Protocol

Following the initial TURBT and subsequent pathological evaluation, management decisions, including repeat TURBT, selection of intravesical therapy, and follow-up protocols, were guided by the EAU guidelines. The SWOG protocol was adopted as the BCG protocol, and adequate BCG therapy is defined as a patient receiving at least five of the six induction instillations, along with at least one maintenance cycle

consisting of two of the three instillations, within 6 months (6,7).

All pathology specimens were reviewed and reported by genitourinary pathologists. Tumor grade was assigned using the 2004/2016 World Health Organization grading system.

Follow-up and Outcome Assessment

Follow-up was conducted using cystoscopy and cytology according to EAU guidelines. Recurrence was defined as the pathological confirmation of a new tumor during follow-up. Progression was defined as the detection of a pT2 or higher stage tumor on follow-up in patients with confirmed recurrent disease. The primary outcome of this study was to assess the oncologic outcomes of HR and VHR NMIBC patients receiving adequate BCG therapy.

Statistical Analysis

To examine relevant clinical characteristics and identify factors associated with disease recurrence and progression, we employed IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Data distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were analyzed with either Pearson's chi-square test for larger samples or Fisher's exact test for smaller samples. Additionally, Cox proportional hazards regression models were implemented to determine independent predictors for both disease recurrence and progression. Kaplan-Meier curves were produced to calculate survival rates for disease progression and to evaluate the differences in survival curves between groups using the log-rank test. All statistical tests were performed with a significance level set at $p < 0.05$.

RESULTS

Patient Characteristics

The study cohort consisted of 211 patients with HR or VHR NMIBC. Of these, 144 (68.2%) were classified as HR and 67 (31.8%) as VHR according to the EAU NMIBC risk calculator. The median follow-up duration was 45 months (range: 12-102 months), and Table 1 summarizes the demographic, clinical, and pathological characteristics of the two groups.

Significant differences were observed between the HR and VHR groups in several baseline characteristics. Patients in the VHR group were significantly older, with a greater proportion aged 70 years or older (61.2% vs. 27.8%; p<0.001). The VHR group also had a higher proportion of patients with multiple tumors (76.1% vs. 60.4%; p=0.026), larger tumors (≥3cm: 89.6% vs. 72.2%; p=0.005), pT1 stage tumors (92.5% vs. 74.3%; p=0.002), concomitant CIS (25.4% vs. 3.5%; p<0.001), variant histology (28.4% vs. 0.7%; p<0.001), lymphovascular invasion (11.9% vs. 0%; p<0.001), and tumor necrosis (22.4% vs. 6.9%; p=0.001). There were no statistically significant differences between the groups regarding gender (p=0.235), smoking status (p=0.751), or the need for a second transurethral resection (p=0.192).

Oncologic Outcomes

Recurrence was observed in 48 patients (33.3%) in the HR group and 25 patients (37.3%) in the VHR group (p=0.572). Progression occurred in 15 patients (10.4%) in the HR group and 6 patients (9%) in the VHR group (p=0.741). There was no statistically significant difference in recurrence or progression rates between the two risk groups.

Univariate analysis revealed factors affecting recurrence: risk group and tumor number (Table 2). On the other hand, in multivariate analysis, tumor number (multiple) (HR: 2.545, %95 CI 1.405 -4.609, p=0.002) was found to be significant. There were no statistically significant parameters in the regression analysis for factors affecting progression (Table 3).

Figure 2 shows Kaplan–Meier curve for reccurence-free survival (RFS). The p value of the log-rank method was 0.020 and the chi-square value was 5.381. The estimated RFS time was 77.7 ± 2.6 months in HR group and 64.2 ±4.7 months in VHR group. The 5-year RFS rate was 75% in the HR group and 56% in the VHR group (p=0.003). This indicates a statistically significant difference in RFS between the two risk groups, with the HR group experiencing a more favorable outcome.

Figure 3 shows the Kaplan–Meier curve for progression-free survival (PFS). The p value of the log-rank method was 0.572 and the chi-square value was 0.319. The estimated PFS time was 92.5 ± 2.2 months in HR group and 88.5 ± 3.9 months in VHR group. The 5-year PFS rate was 91% in the HR group and 86% in the VHR group (p=0.311). This indicates no statistically significant difference in PFS between the two risk groups.

Table 1. Demographic, clinical, and pathological characteristics of the groups

	High-Risk (n=144)	Very High-Risk (n=67)	p value
Age, n (%)			**<0.001**
<70	104 (72.2)	26 (38.8)	
≥70	40 (27.8)	41 (61.2)	
Gender, n (%)			0.235
Female	24 (16.7)	7 (10.4)	
Male	120 (83.3)	60 (89.6)	
Smoking status, n (%)			0.751
Never	21 (14.6)	12 (17.9)	
Exsmoker	74 (51.4)	35 (52.2)	
Smoker	49 (34)	20 (29.9)	
Number of tumors, n (%)			**0.026**
Single	57 (39.6)	16 (23.9)	
Multiple	87 (60.4)	51 (76.1)	
Maximum tumor size, n (%)			**0.005**
<3cm	40 (27.8)	7 (10.4)	
≥3cm	104 (72.2)	60 (89.6)	
Tumor stage, n (%)			**0.002**
pTa	37 (25.7)	5 (7.5)	
pT1	107 (74.3)	62 (92.5)	
Concomitant carcinoma in situ, n (%)			**<0.001**
No	139 (96.5)	50 (74.6)	
Yes	5 (3.5)	17 (25.4)	
Presence of variant histology, n (%)			**<0.001**
No	143 (99.3)	48 (71.6)	
Yes	1 (0.7)	19 (28.4)	
Presence of lymphovascular invasion, n (%)			**<0.001**
No	144 (100)	59 (88.1)	
Yes	0	8 (11.9)	
Presence of tumor necrosis, n (%)			**0.001**
No	134 (93.1)	52 (77.6)	
Yes	10 (6.9)	15 (22.4)	
Second transurethral resection, n (%)			0.192
No	40 (27.8)	13 (19.4)	
Yes	104 (72.2)	54 (80.6)	
Recurrence, n (%)			0.572
No	96 (66.7)	42 (62.7)	
Yes	48 (33.3)	25 (37.3)	
Progression, n (%)			0.741
No	129 (89.6)	61 (91)	
Yes	15 (10.4)	6 (9)	

Table 2. Univariate and multivariate analysis: Factors affecting recurrence

	Univariate Analysis		Multivariate Analysis	
	HR (%95 CI)	**p value**	**HR (%95 CI)**	**p value**
Risk group (Very high vs high)	1.762 (1.082 – 2.870)	**0.023**	1.476 (0.900 – 2.420)	0.123
Age (≥70 vs <70 years)	1.176 (0.725 – 1.907)	0.511		
Gender (male vs female)	0.945 (0.484 – 1.845)	0.868		
Number of tumors (multiple vs single)	2.740 (1.526 – 4.917)	**0.001**	2.545 (1.405 – 4.609)	**0.002**
Tumor size (≥3 cm vs < 3 cm)	1.591 (0.886 – 2.858)	0.120		
Tumor stage (pT1 vs pTa)	0.903 (0.445 – 1.832)	0.778		
Accompanying CIS (yes vs no)	1.260 (0.577 – 2.754)	0.562		
Variant histology (yes vs no)	1.196 (0.479 – 2.981)	0.702		
Lymphovascular invasion (yes vs no)	1.796 (0.563 – 5.731)	0.323		
Tumor necrosis (yes vs no)	1.829 (0.899 – 3.721)	0.096		

HR: High risk, **CIS:** carcinoma in situ

Table 3. Univariate analysis: Factors affecting progression

	Univariate Analysis	
	HR (%95 CI)	**p value**
Risk group (Very high vs high)	1.314 (0.507 – 3.403)	0.574
Age (≥70 vs <70 years)	1.047 (0.420 – 2.608)	0.921
Gender (male vs female)	3.125 (0.419 – 23.311)	0.266
Number of tumors (multiple vs single)	2.833 (0.952 – 8.434)	0.061
Tumor size (≥3 cm vs < 3 cm)	2.190 (0.643 – 7.461)	0.210
Accompanying CIS (yes vs no)	1.183 (0.275 – 5.090)	0.821
Variant histology (yes vs no)	0.786 (0.105 – 5.891)	0.815
Tumor necrosis (yes vs no)	1.302 (0.298 – 5.686)	0.725

HR: High risk, **CIS:** carcinoma in situ

DISCUSSION

This retrospective study evaluated the oncologic outcomes of HR and VHR NMIBC patients treated with adequate BCG therapy, aiming to address the knowledge gap regarding the applicability of the EAU risk stratification in this specific population. Our findings revealed several key observations.

Firstly, despite the VHR group exhibiting more aggressive tumor characteristics at baseline, including older age, larger and multiple tumors, higher pT stage, presence of CIS, variant histology, lymphovascular invasion, and tumor necrosis, we did not observe a statistically significant difference in overall recurrence or progression rates between the HR and VHR groups. This suggests that BCG therapy may effectively mitigate the increased risk associated with these adverse pathological features, at least in terms of overall recurrence and progression rates. This finding is crucial, as it indicates that BCG remains a valuable treatment option even for patients classified as VHR according to the EAU criteria. Furthermore, EAU risk groups may not accurately reflect disease progression in patients classified as VHR who received immunotherapy. EAU risk stratification reports a 40% probability of progression at five years for the VHR group, potentially leading to recommendations for immediate radical cystectomy (4). However, our findings suggest that this risk estimation might be lower, particularly

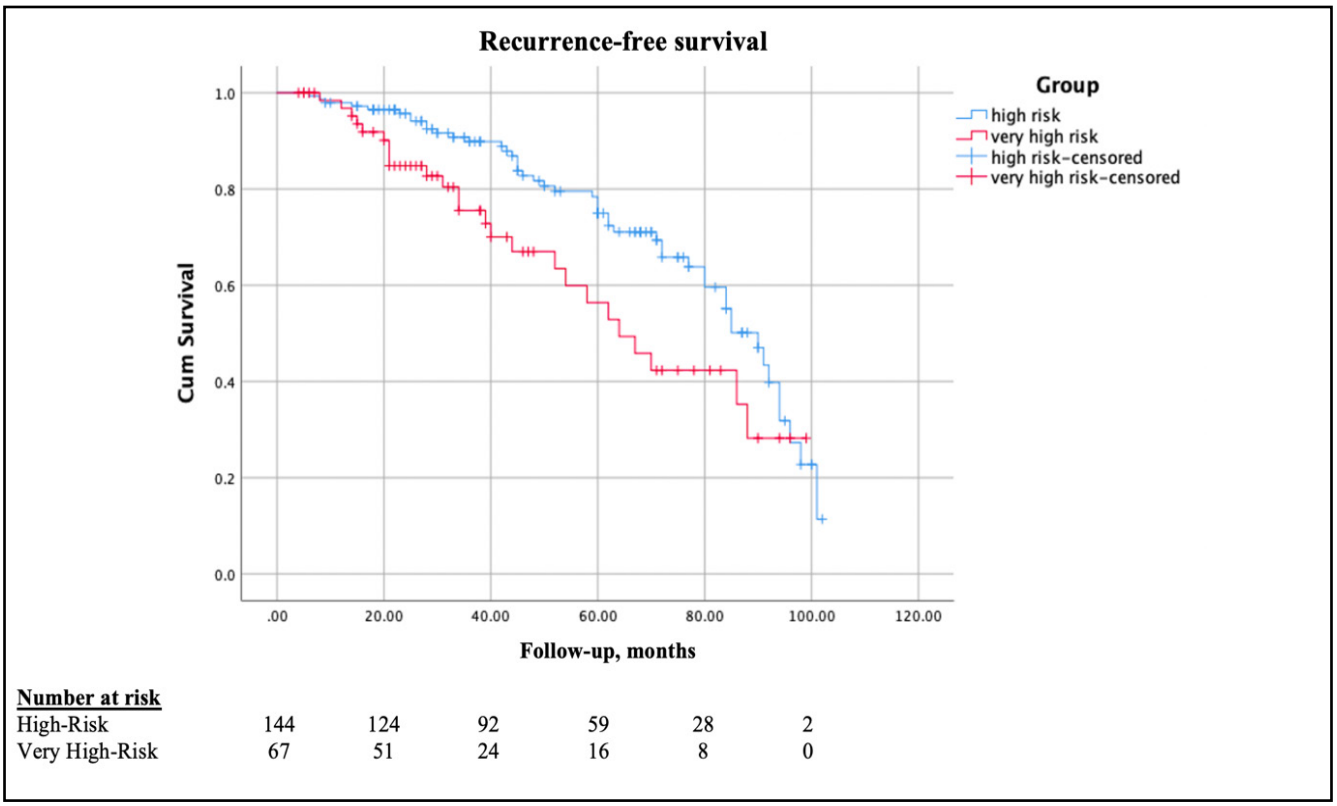

Figure 2. Kaplan-Meier analysis of recurrence-free survival with BCG treatment

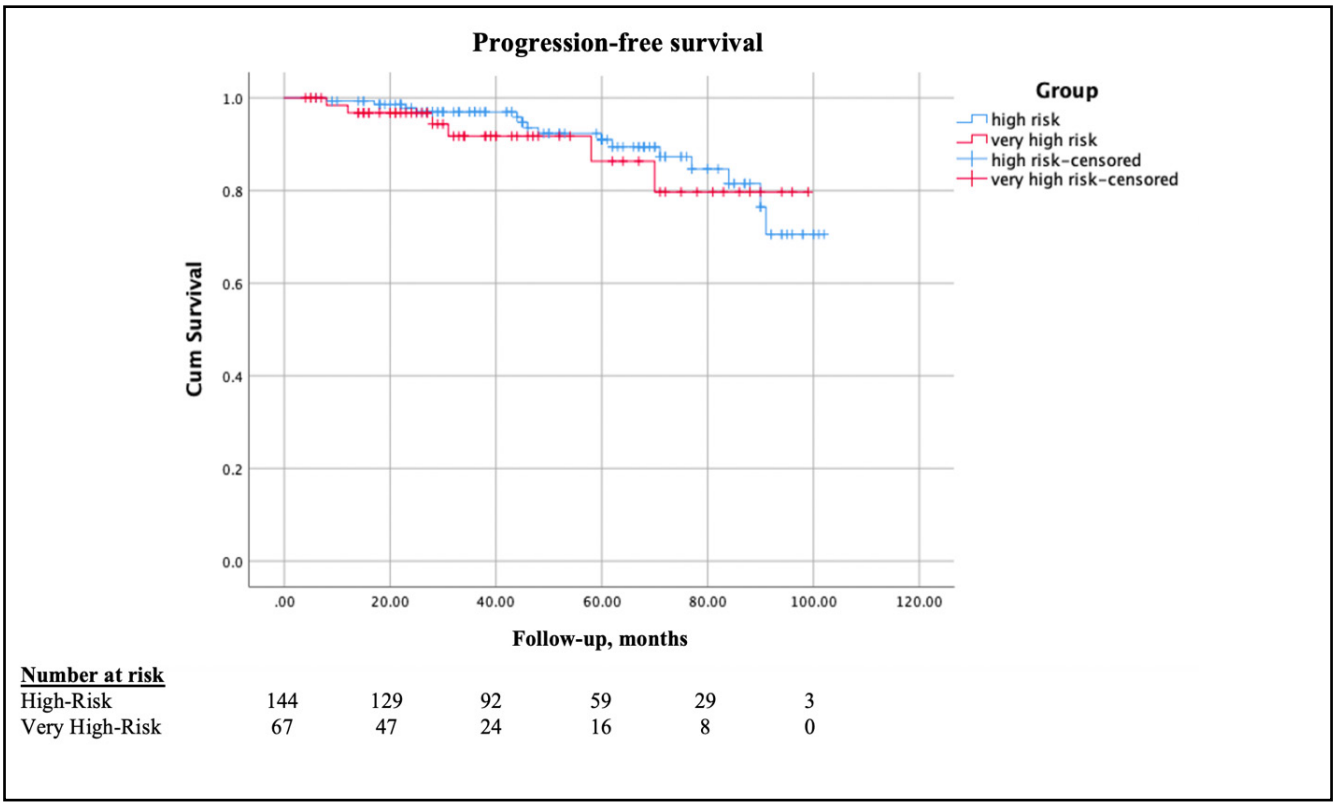

Figure 3. Kaplan Meier analysis of progression-free survival with BCG treatment

for patients receiving BCG therapy. This highlights the complexity of clinical decision-making for HR and VHR NMIBC patients. Studies have shown the efficacy of BCG therapy for preventing recurrence compared to intravesical chemotherapy, especially in the setting of maintenance treatment regimens (8). While some studies, such as the one by Schmidt et al., have not observed a statistically significant difference in disease progression or survival outcomes between BCG and intravesical chemotherapy (9), BCG therapy is generally recognized to delay or prevent progression (10). Lobo et al. recently reported lower disease progression rates in a study investigating the effect of BCG therapy on risk stratification. Patients in the VHR group who received induction BCG therapy (6.9%) and those who completed adequate BCG therapy (4.0%) demonstrated significantly lower progression rates at one year compared to the predicted rates of 16.0% according to the EAU risk stratification system. This trend persisted for five years, with lower progression rates observed in both the HR and VHR groups who received BCG therapy compared to the predicted EAU rates (7.4% vs. 9.6% and 16.7% vs. 40.0%, respectively) (10). Also, another recent study found a 25.8% progression risk for the VHR group at 5-year follow-up (11). Our study's findings regarding the impact of BCG therapy on disease progression align with those reported in these studies, and a lower progression rate was observed in patients receiving BCG therapy compared to the rates predicted by the EAU risk stratification system.

In line with these observations, our analysis revealed no significant difference in PFS among patients classified as HR and VHR (91% vs 86%, p=0.311, respectively) who were treated with BCG. This observation underscores the potential therapeutic role of immunotherapy in the VHR patient population. Consequently, our findings suggest re-evaluation regarding the necessity of immediate radical cystectomy for patients classified as VHR, particularly considering the significant morbidity and mortality associated with this surgical intervention. Contieri et al. also investigated the accuracy of the new EAU NMIBC risk calculator, specifically evaluating its performance in a study including patients with T1 high-grade disease who underwent a second transurethral resection followed by BCG therapy (12). Their analysis revealed a five-year PFS rate of 68.2% for the entire cohort, with a further decrease to 59.9% within the VHR group. These findings led Contieri et al. to conclude that the new risk groups might underestimate the effectiveness of BCG therapy, potentially due to the inclusion of an age threshold within the risk stratification model (12). Notably, their study did not detect a significant impact of the 70-year age limit on the outcomes within their patient population. Similarly, Krajewski et al. reported an overestimation of progression rates within a cohort of high-grade NMIBC patients, observing a five-year PFS of 82.3% (13). For patients receiving BCG therapy, the CUETO risk scoring model remains a commonly employed tool for predicting disease progression (14). However, the inherent heterogeneity of BCG treatment regimens presents a significant challenge to accurate prediction.

The present study is not without its limitations. The retrospective design introduces inherent biases, including selection bias and potential data inconsistencies. Additionally, the study was conducted at a single institution, and the relatively small sample size, particularly in the very high-risk group, may limit the study's findings.

CONCLUSION

The findings of our study suggest that BCG treatment reduced the risk of progression in VHR groups. Furthermore, the new risk classification overestimates the rate of progression in patients receiving BCG therapy. These findings underscore the necessity of incorporating BCG treatment status into treatment decision-making algorithms for this patient population. In light of these findings, further evaluation and the development of a revised classification system are imperative.

Authorship Confirmation Statement: All authors contributed to the study conception and design, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interests: No potential conflict of interest relevant to this article was reported.

Ethical Approval: Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee Approved by the Ethics Committee. (Approval No: 2022/0560). All patients participating in the study were informed about the study, and their informed consent was obtained.

REFERENCES

1. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234-241. https://doi.org/10.1016/j.eururo.2012.07.033
2. Compérat E, Larré S, Roupret M, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch. 2015;466(5):589-594. https://doi.org/10.1007/s00428-015-1739-2
3. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin. Eur Urol. 2016;69(1):60-69. https://doi.org/10.1016/j.eururo.2015.06.045
4. Sylvester RJ, Rodríguez O, Hernández V, et al. Erratum to "European Association of Urology (EAU) Prognostic Factor Risk Groups for Non-muscle-invasive Bladder Cancer (NMIBC) Incorporating the WHO 2004/2016 and WHO 1973 Classification Systems for Grade: An Update from the EAU NMIBC Guidelines Panel" [Eur. Urol. 79(4) (2021) 480-488]. Eur Urol. 2023;83(5):e140-e141. https://doi.org/10.1016/j.eururo.2023.02.007
5. Babjuk M, Burger M, Capoun O, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). Eur Urol. 2022;81(1):75-94. https://doi.org/10.1016/j.eururo.2021.08.010
6. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, Sarosdy MF, Bohl RD, Grossman HB, Beck TM, Leimert JT, Crawford ED. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000 Apr;163(4):1124-9.
7. Kamat AM, Sylvester RJ, Böhle A, et al. Definitions, End Points, and Clinical Trial Designs for Non-Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group. J Clin Oncol. 2016;34(16):1935-1944. https://doi.org/10.1200/JCO.2015.64.4070
8. Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol. 2010;57(5):766-773. https://doi.org/10.1016/j.eururo.2009.12.024
9. Schmidt S, Kunath F, Coles B, et al. Intravesical Bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2020;1(1):CD011935. Published 2020 Jan 8. https://doi.org/10.1002/14651858.CD011935.pub2
10. Lobo N, Hensley PJ, Bree KK, et al. Updated European Association of Urology (EAU) Prognostic Factor Risk Groups Overestimate the Risk of Progression in Patients with Non-muscle-invasive Bladder Cancer Treated with Bacillus Calmette-Guérin. Eur Urol Oncol. 2022;5(1):84-91. https://doi.org/10.1016/j.euo.2021.11.006
11. Ślusarczyk A, Garbas K, Pustuła P, Zapała Ł, Radziszewski P. Assessing the Predictive Accuracy of EORTC, CUETO and EAU Risk Stratification Models for High-Grade Recurrence and Progression after Bacillus Calmette-Guérin Therapy in Non-Muscle-Invasive Bladder Cancer. Cancers (Basel). 2024;16(9):1684. Published 2024 Apr 26. https://doi.org/10.3390/cancers16091684
12. Contieri R, Hurle R, Paciotti M, et al. Accuracy of the European Association of Urology (EAU) NMIBC 2021 scoring model in predicting progression in a large cohort of HG T1 NMIBC patients treated with BCG. Minerva Urol Nephrol. 2023;75(2):180-187. https://doi.

org/10.23736/S2724-6051.22.04953-9

13. Krajewski W, Aumatell J, Subiela JD, et al. Accuracy of the CUETO, EORTC 2016 and EAU 2021 scoring models and risk stratification tables to predict outcomes in high-grade non-muscle-invasive urothelial bladder cancer. Urol Oncol. 2022;40(11):491.e11-491.e19. https://doi.org/10.1016/j.urolonc.2022.06.008

14. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009;182(5):2195-2203. https://doi.org/10.1016/j.juro.2009.07.016